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Introduction

Most reports of treatment of lymphosarcoma (LSA) in domestic animals have involved canine and feline LSA. The disease in cats differs from that in dogs in that feline LSA is caused by a contagious retrovirus. Controversy has existed as to whether feline leukemia virus (FeLV) positive cats with LSA should be treated because of their danger to other cats, or because of the controversial question of a human health hazard. There has been no proven danger to people, and 30% of cats with LSA are FeLV negative.[1] Some owners elect chemotherapy for their cats regardless of potential risks. As a result of this increasing awareness of pet owners to the potential benefits to be gained by chemotherapy, the practicing veterinarian must be able to skillfully administer chemotherapy to pets who have developed cancer.

The purpose of this paper is to describe the principles of chemotherapy as currently understood and to integrate these principles with the clinical management of the most common malignant disorder of the cat; feline LSA.[2]

Chemotherapy of the Cancer Patient — General Principles

Interrelationships: Tumor, Host and Drug

The veterinarian, when utilizing cancer chemotherapeutics, should always keep in mind the interactions between the tumor, host, and drugs. These interactions are: (a) disease, i.e., the effect(s) of the tumor on the host; (b) therapy, the effect(s) of the drug on the tumor; (c) toxicity, the effect(s) of the drug on the host. The dominant factor or factors in this relationship determine the final outcome of the animal receiving cancer chemotherapy. For example, an excellent response to therapy encompasses remission of signs or symptoms of disease without the impairment of normal functions of the host due to toxicity. The quality of survival, determined by these interactions, is very important to the client and veterinarian since euthanasia exists as an alternative.

Selection of Patient for Chemotherapy

Considerable care should be taken in the selection of cases suitable for chemotherapy so that worthwhile regressions are obtained in as many instances as possible. Chemotherapy is the most suitable form of therapy for patients with tumors which are not amenable to surgery or radiation therapy. Thus, patients with disseminated tumors such as leukemia, lymphosarcoma, multiple myeloma and other hemopoietic tumors or patients with malignant solid tumors which may have metastasized should be considered for chemotherapy.[3,4,5] Carcinomas and sarcomas in which the majority of the tumor has been destroyed by surgery, cryosurgery, or radiotherapy but have high risks of recurrence and/or metastases can also be candidates for chemotherapy.[4,6]

In general, chemotherapeutic agents give the best results when used to treat rapidly growing tumors, and are much less effective when the tumor is growing slowly and contains many dividing cells.[3,7] Malignant cells in hemopoietic cancers have a very high growth rate compared to solid tumors and normal tissues and are thus especially susceptible to anticancer drugs. It is also thought that solid tumors develop primary and secondary resistance to drugs earlier than other neoplasms.[6] In order to obtain a complete cure it is essential that all the malignant cells in the body be killed. The smaller the number of malignant cells present, the greater is the chance of obtaining a 100% kill. Thus chemotherapy should be started as soon as possible and used as an adjunctive therapy to surgery

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and radiation therapy whenever possible. Another fact which lends support to the debulking of tumors prior to initiation of chemotherapy is that in the center of large tumors drug penetration is low due to the poor blood supply.

The effectiveness of chemotherapy in treating tumors in animals cannot be accurately estimated until a histological identification is made so that the biological behavior of the tumor can be assessed. However, chemotherapy is useful for those tumors in which the results of surgery or radiation therapy are poor as established by clinical trials.[3,5]

Until recently, there has been considerable reluctance to administer toxic drugs to patients apparently clinically free of tumor after surgery or radiotherapy. However, there is strong evidence that some such patients are not free of malignant cells and that aggressive chemotherapy before metastases are clinically detectable increases the chances of survival. The problem is to identify those patients with clinically undiscernable metastasis who would benefit from adjunctive therapy. The development of biochemical or immunological assays for the presence of tumor cells would therefore be an important contribution to the control of tumors by chemotherapy. Until such assays are developed the selection of patients for adjuvant chemotherapy can be based only on an estimation of the degree of malignancy of the type of primary tumor involved.

Before any animal is selected to receive chemotherapy, the clinician must be able to meet the following standards in order to utilize chemotherapeutic agents safely:

(1) Establish a histological diagnosis of malignancy and a known sensitivity to antineoplastic drugs.
(2) Be familiar with the drugs and their potential toxicity.
(3) Use safe dosage schedules established for dogs and cats.
(4) Be able to monitor toxicity at regular intervals.
(5) Be able to evaluate an adequate response.
(6) Establish a willingness on the part of the client to cooperate fully with the veterinarian during a carefully planned therapy program.

The decision to initiate therapy or select which drugs may be best administered may be influenced by the pre-treatment evaluation of the patient. A complete history should be taken to establish if any previous therapy has been given or if there has been any other recent illness which may influence the effectiveness of the drugs. A complete physical examination along with baseline hematological data such as complete blood counts, platelet counts, urinalaysis and liver and kidney function tests are mandatory. Other tests such as bone marrow examination or special radiological procedures may be needed to completely evaluate the extent of disease or underlying complications.

Cell Kinetics

A knowledge of the cell cycle or the proliferative state of the cell population is important for understanding the cytotoxic effects of cancer chemotherapy. The cell cycle can be defined as an orderly sequence of events occurring during the time interval between one cell division and the next division.[3] The cell cycle is divided into the following phases: mitosis (M), postmitotic growth in which RNA and protein synthesis occur prior to DNA synthesis (G), resting or nonproliferative phase for differentiated cells (G_0), new DNA synthesis (S), and RNA and protein synthesis prior to mitosis (G_2). Cell populations differ in relationship to DNA snythesis and mitosis in that some cells continuously move through the cell cycle; other cells leave the cycle but can be induced to synthesize DNA and divide by certain stimuli; and finally, some cells will leave the cycle permanently and will die without further division.

Normal cells have four basic properties: (1) ability to proliferate; (2) capacity for self-renewal; (3) ability to differentiate; and (4) sensitivity to regulatory mechanisms.[5] Malignant cells have the first two properties and differentiation may be present but abnormal. The main difference between normal and malignant cells is response to regulation; in malignant cells this property is either greatly reduced or completely absent. The ideal treatment would bring about maximum normal cell survival and minimal tumor cell recovery.

The response of cells to drugs depends on the mechanism of action of the drug and the position of the cell in the cell cycle.[3,5] Not only do drugs kill at different stages of the cycle, but if a drug can be used to arrest cells at one stage of the cycle, a second drug killing at maximum effect at this stage can then be instituted.[4]

Anticancer drugs can be divided into six classes according to their mechanism of action.[3]

1. Hormones were one of the first types of chemotherapeutic agents to be used against tumors but their mechanism of action is not yet completely understood. It is thought that they may act by interfering with cell membrane receptors that stimulate growth.
2. The alkylating agents were the first synthetic an-

titumor agents to be used. They are thought to act by crosslinking cellular DNA by the formation of a covalent bond, thus impeding its ability to act as a template for RNA or DNA synthesis.
3. The antimetabolites interfere with the biosynthesis of nucleic acids by substituting for normal metabolites and by inhibiting normal enzymatic reactions.
4. Antibiotics are thought to bind nonspecifically to cellular DNA and inhibit transcription.
5. Mitotic inhibitors destroy the mitotic spindle of the cell and prevent cell division.
6. Miscellaneous drugs are those which act by a combination of mechanisms or which do not act in any of the ways described above or whose mechanisms of action is at present unknown.

Expression of Drug Doses

The objective of chemotherapy is to dose to maximum efficacy with minimum toxicity. The utilization of drugs and expression of their dosages on a body weight basis (e.g., mg/kg) is a common practice in veterinary and human medicine. In the human adult, there may be justification for standardization of dosages of the majority of drugs by this method. However, this has not proved to be a valid practice in pediatrics nor with the use of antineoplastic agents. The same may prove true for other drugs which are now routinely given on a sliding-dosage scale.

A comparison of the toxicity of anticancer agents has been made in the mouse, rat, hamster, dog, monkey, and human (Freireich et al., 1966). There were large differences in the maximum tolerated dose if it was based on mg/kg body weight, but the dose was found to be approximately the same in all species if based on surface area — mg/meter squared (mg/M^2).[4] This method ensures adequate dosing in small dogs and cats and precludes overdosing in large dogs.

The fate of systemically administered drugs depends on many factors and may include the following: route, dose, and speed of administration; mechanism and distribution of intra -and/or extracellular uptake of the drug; presence of other drugs or substances which interact or interfere; extent, rate, mechanism(s), and tissue(s) of metabolism and excretion of the drug; total body fluid and/or blood volume; and others.[8] Thus, the pharmacokinetics of most drugs depend on one or more physiologic processes of the host.

The basal metabolic rate (BMR) perhaps best reflects most of these physiologic functions in the normal animal. But its determination is tedious and is often impossible to obtain accurately and quickly. The BMR has been shown to be best approximately by the body surface area (BSA).[8] The BSA of an animal can be easily determined by the formula:

$$A = \frac{K \times (W)^{\frac{2}{3}}}{10^4}$$

where A is the body surface area in square meters, W is the body weight in grams and K is a constant (10.0 for cats and 10.1 for dogs). In addition, the dose of a drug in mg/kg can be easily converted to mg/M^2 by the formula:

$$(\text{Dose in } mg/M^2) = k_f \times (\text{Dose in } mg/kg)$$

where k_f is a conversion factor given by the formula:

$$k_f = \frac{(wt)^{1/3} \times 10^2}{K}$$

where wt is the body weight in kilograms and K is the constant (10.0 for cats and 10.1 for dogs).

Conversion charts for directly determining the BSA in M^2 have been provided by others.[3,4]

Combination Therapy

It has been found that many chemotherapeutic agents used alone can produce only limited remissions. Combination chemotherapy, that is, when several different drugs are used together (or in sequence), has proved to be more effective than single drug therapy.[1,3,5,9-11] Drugs to be used in combination chemotherapy should have an existing proven effect — either crytostatic or cytotoxic — against tumors when used alone, or should be capable of arresting the neoplastic cell at a particular stage of the cell cycle when it is susceptible to other drugs. Four basic principles underlie the design of combination chemotherapy protocols. These are: (1) the fraction of tumor cells killed by one drug is independent of the fraction killed by another drug; (2) drugs with different mechanisms of action should be chosen so that the antitumor effects will be additive; (3) since different classes of drugs have different toxicities, the toxic effects will not be additive and each drug can be used at its maximum dose and (4) use only drugs with known activity against a specific neoplasm.[3,5,9,10] Drugs that show some efficacy when used in certain species for the treatment of LSA are vincristine, cyclophosphamide, L-asparaginase, doxorubicin HCL and prednisone. Chlorambucil, antimetabolities including

methotrexate and cytosine arabinoside, 6-mercaptopurine, and 6-thionguanine have been advocated in combination protocols but have not shown antitumor activity as single agents. Other drugs have been used in drug-resistant or relapsed LSA cases. These include dacarbazine, procarbazine, CCNU, Cis-platinum, and bleomycin sulfate. Attempts to reinduce remission with these drugs have been discouraging.[11] It should be noted that because of the cat's unique hepatic metabolism, not all of these drugs can be used safely in this species.

Experimental tumor systems have shown that the emergence of populations resistant to the individual drugs can be delayed or suppressed if a combination of several drugs is used and therefore prolong the time necessary for these cells to produce clinically apparent disease.[4,5] When the toxic effects of chemotherapeutic agents used in a given protocol do not overlap too greatly, it is possible to use almost maximum doses of each individual drug without greatly increasing toxicity.

Combination chemotherapy is most efficacious when given in intensive intermittent courses rather than in continuous low dose form. There tends to be greater tumor cell death and much less immunosuppression. Intermittent, intensive chemotherapy may augment the endogenous cellular immune response to tumor cells during the recovery period.

Toxicity and Complications

Most chemotherapeutic drugs are toxic to all dividing cells and the distinction between therapeutic and toxic doses is often very fine. Thus, the difference in susceptibility between normal and tumor cells governs the choice of drug, dose, and effectiveness of chemotherapy. The toxic side effects may be slight: mild alopecia, anorexia, vomiting and diarrhea may necessitate only a temporary withdrawal of chemotherapy. Side effects such as thrombocytopenia, leukopenia, anemia, and gastrointestinal bleeding are usually mild but in some cases can be so severe that chemotherapy may have to be discontinued permanently.[5] It is essential that all animals receiving chemotherapy be monitored frequently.

Monitoring should include a thorough physical examination, complete blood cell count and platelet count every 7 to 10 days. Serum enzyme levels and renal function should be monitored as needed or every several months. In no case should the total white cell count be allowed to fall below $3000/mm^3$.[3,5] Transfusion facilities and antibiotics should be available to support the patient in case of severe bone marrow depression. If complete monitoring facilities are not available then chemotherapy should be limited to the administration of hormones where the risk of severe side effects are low. The drug L-asparaginase could also be used in this situation; keeping in mind that anaphylaxis has been known to occur with its use.

It is very important for the veterinarian to remember that once a drug (except methotrexate) has been administered, there is nothing that can neutralize its action or prevent serious delayed side effects. A thorough explanation to the client about potential side effects before the use of anticancer drugs will help the client observe the patient at home and detect the earliest signs of complications, thus allowing early treatment.

Generally, the majority of the anticancer drugs cause myelosuppression and immunosuppression but a few of the drugs have unique toxic side effects. Cyclophosphamide and vincristine will be discussed later. With 5-fluorouracil bizzare central nervous system reactions have been seen. The reactions are characterized by apparent hallucinations, hyperexcitability, fright, and severe personality change. This drug is highly toxic to cats and should not be given to cats under any circumstances.

Side effects indirectly related to the drugs are those due to rapid tumor cell breakdown and can lead to abnormal hepatic or renal function. Local reactions such as pain, edema, inflammation, and abscess formation or tissue necrosis can occur as the tumor cells die and are eliminated from the body.

Toxic Side Affects of Agents Commonly used for Therapy of Lymphorsarcoma

Vincristine. This drug is a plant alkaloid. Its mechanisms of action is related to an arrest of cell division in metaphase. It appears to exhibit minimal myelosuppression compared with other agents. A peripheral neuropathy may occur at chronic, high doses. This may manifest itself in any of several ways; (1) a noticeable change in the animal's gait, (2) constipation secondary to colonic atony, or (3) voice changes due to laryngeal dysfunction. These are uncommon but ususally reversible conditions. Perivascular infiltration of the agent will cause severe tissue inflammation and probable loss of local venous access.

L-asparaginase. This drug is a bacterial enzyme that (in some cases) exploits the inability of malignant lymphoblasts to produce L-asparagine by destroying extracellular supplies of this essential amino acid. Because normal cells can produce L-asparagine, little to no host toxicity is produced by this effect. However, bacterial cell products contaminating the agent can result in an anaphylactic

reaction occurring in animals within either their first treatment exposure or after repeated exposure to L-asparagine. Thus, clinicians administering L-asparaginase to patients must be prepared to control potential allergic reactions.

Cyclophosphamide. This alkylating agent causes damage to nucleic acids, interfering with DNA replication and the transcription of RNA. The drug's major toxic effects are to rapidly proliferating normal tissues such as bone marrow and intestinal mucosa. Thus, leukopenia, thrombocytopenia, vomiting and diarrhea are possible complications. Most authors suggest temporarily decreasing or discontinuing the use of myelosuppressive drugs if the pretreatment leukocyte count is below 3500 to 4000 cells/mm^3.[1,9]

In addition to these toxicities, cyclophosphamide may produce hemorrhagic cystitis secondary to urinary excretion of the drug's inactive metabolities. The likelihood of this is probably directly related to the length of time the metabolities remain in the urinary bladder. An animal able and willing to urinate and one that maintains a normal or increased urine output (such as a patient being given glucocorticoids) is thus less likely to develop a drug related cystitis. Cats develop cyclosphamide induced cystitis much less frequently than dogs.

Cytosine arabinoside. This drug is metabolized to a necleoside analogue, acting as a competitive inhibitor of DNA polymerase. It is considered to be an antimetabolite drug. The major toxicities from the agent are myelosuppression and intestinal mucosal damage, which are similar to those occuring with cyclophosphamide. Therefore, if the two drugs are used in the same protocol, the clinician and owner should be aware of the potential for additive toxic effects.

Methotrexate. Also an antimetabolite, this drug is one of the first folic acid inhibitors introduced for antitumor therapy. It has potent toxic effects similar to those of other antimetabolities, including cytosine arabinoside.

Prednisone. In addition to their palliative benefits in the animal with debilitating malignant disease, corticosteroids are employed as lymphocytotoxic agents in patients with lymphoreticular tumors. Prednisolone may be used instead in equivalent dosages. In the high daily doses used, several adverse effects are possible. These include suppression of the hypothalamic-pituitary axis, polyuria, polyphagia, and, like most the anticancer drugs, immunosuppression. Alternate-day administration may decrease some of these complications.[9]

Chemotherapeutic Protocols of the Management of Lymphosarcoma

Once the decision is made that the patient is a good candidate for chemotherapy, the initiation of treatment is preceded by a discussion with the owner concerning prognosis and an estimate of costs, both in time and money. In animals treated with standard antitumor protocols, at least one fact is clear: Patients that respond with a complete remission tend to live longer and enjoy a better quality of life than those that fail to respond completely. Thus, for example, cats with LSA originating in the mediastinum, alimentary tract, or peripheral lymph nodes (that is, forms that show a marked sensitivity to cytotoxic therapy) appear to have a better prognosis than cats presenting with other forms, such as primary leukemia or central nervous system LSA.[9] The median duration or remission reported for cats responding to cytotoxic chemotherapy has varied from 4 to 28 months, depending on the form and stage of the disease.

Several specific protocols of tumor management have been reported.[1,2,9]

Tumor Resistance to Chemotherapy

The development in tumor cells of varying degrees of resistance to drugs is one of the limiting factors in tumor chemotherapy. If this phenomenon did not exist many tumors could probably be kept under control indefinitely by chemotherapy. Unfortunately, however, resistance to drugs develops in all tumors to varying degrees while normal cells which are sensitive to antitumor drugs do not develop resistance. It is not known whether drug resistant cells pre-exist in drug sensitive tumors or whether resistant cells appear as the result of drug induced mutations. Some of the most important ways in which tumor cells may acquire resistance are: (1) the development of alternative metabolic pathways (sometimes seen with L-asparaginase); (2) the development of repair mechanisms to correct the damage done by the drug; (3) destruction of the drug by the cell; (4) changes in the permeability of the cell membrane; (5) tumor cells entering the resting (G°) phase of the cell cycle; and (6) deletion of cellular drug activation mechanisms.[3,5,6] Some tumors are naturally resistant to chemotherapy. In many cases the reasons for this natural (as opposed to acquired) resistance are unknown. In other cases drug resistance is the result of the anatomical location of the tumor. For example, most chemotherapeutic agents cannot cross the blood-brain barrier; thus primary or secondary metastatic neoplasms in the central nervous system survive the

intended actions of these drugs.

The development of drug resistant tumors can be limited by the use of combination chemotherapy. In addition to the additive antitumor effects of combined drug therapy, some tumors become more susceptible to one drug as they become more resistant to another.[3] This phenomenon has been observed in some animal tumors but is unfortunately rather rare.

Summary

As pet owners become more knowledgeable about the various options available to them concerning their pet stricken with a neoplastic disease, veterinarians must be able to respond and outline a treatment regimen which is both efficacious and economical. By utilizing the principles outlined in this paper, the veterinarian will have a foundation upon which to build according to the specific needs and desires of his clientele.

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